I. AMENDMENT

Please make the following amendments:

In the claims:

Please cancel claims 7, 14, 22, and 29, without prejudice.

Please amend claims 1, 9, 16 and 24 as follows:

A1 SubB1

1. (Amended) A method for detecting polymorphisms in a uridine diphosphate glucuronosyltransferase (UGT) gene promoter comprising determining the [number of thymidine-adenine] presence of five or eight (TA) repeats in said promoter, wherein the [number of] the presence of five TA repeats correlates with increased expression of the gene, and the presence of eight repeats correlates with decreased expression of the gene.

A2 SubB2

9. (Amended) A method for detecting polymorphisms in a uridine diphosphate glucuronosyltransferase I (UGT1A1) gene promoter comprising determining the [number of thymidine-adenine] presence of five or eight (TA) repeats in said promoter, wherein the [number of] the presence of five TA repeats correlates with increased expression of the gene, and the presence of eight repeats correlates with decreased expression of the gene.

A3 SubB3

16. (Amended) A method for screening individuals for variation in glucuronidation activity comprising detecting polymorphisms in a uridine diphosphate glucuronosyltransferase (UGT) gene promoter comprising determining the [number of thymidine-adenine] presence of five or eight (TA) repeats in said promoter, wherein the [number of] the presence of five TA repeats correlates with increased expression of the gene, and the presence of eight repeats correlates with decreased expression of the gene.

A4 SubB4

24. (Amended) A method for screening individuals for variation in glucuronidation activity comprising detecting polymorphisms in a uridine diphosphate glucuronosyltransferase I (UGT1A1) gene promoter, the method comprising determining the [number of thymidine-adenine] presence of five or eight (TA) repeats in said promoter, wherein the [number of] the presence of five TA repeats correlates with increased expression of the UGT gene, and the presence of eight repeats correlates with decreased expression of the UGT gene.

Please add the following claims, claims 70-75:

--70. The method of claim 1, 9, 16, 24, 31, 39, 47 or 55, wherein the method comprises determining the presence of five TA repeats in said promoter.

--71. The method of claim 1, 9, 16, 24, 31, 39, 47 or 55, wherein the method comprises determining the presence of eight TA repeats in said promoter.

--72. The method of claim 1, 9, 16, 24, 31, 39, 47 or 55, further comprising determining the presence of six TA repeats, $[TA]_6$, in said promoter.

--73. The method of claim 1, 9, 16, 24, 31, 39, 47 or 55, further comprising determining the presence of seven TA repeats, $[TA]_7$, in said promoter.

--74. The method of claim 31 or 39, wherein the drug is Irinotecan.

--75. The method of claim 31 or 31, wherein the drug is TAS-103. --

II. RESPONSE TO OFFICE ACTION

A. Claims in the case:

Claims 7, 14, 22 and 29 have been cancelled, without prejudice.

Claims 1, 16, 19 and 24 have been amended.

Claims 70 - 75 have been added.

The currently pending claims include 1-6, 8-13, 15-21, 23-28, 30-62 and 70-75.

B. Rejection of Claims 1-30 over Beutler et al.

The Action first rejects claims 1-30 as anticipated under 35 U.S.C. § 102 (a) by Beutler et al.

Applicants would assert that the Beutler et al. publication is not available as prior art against claims 1-30. Applicants have enclosed herewith a Declaration under Rule 131, demonstrating that the present inventors had discovered the existence and demonstrated the relevance of the 5 TA and 8 TA promoter prior to the publication date of the Beutler et al. publication. It is submitted that this declaration, and the accompanying abstract published by the present inventors prior to July, 1998 and reflecting a presentation made by the present inventors prior to July, 1998, makes it clear that the Beutler et al. article is not available under Section 102(a).

C. Rejection of Claims 1-23 as anticipated by Bosma et al.

The Action next rejects claims 1-23 as anticipated under Section 102 (b) by Bosma, et al., (Hepatology, 1992). Applicants would first point out that upon reviewing the Examiner's comments, it appears as though the Bosma, New England Journal of Medicine, Vol. 333, 1995 was intended, and Applicants remarks will be directed to that reference rather than the 1992 reference referred to in the Action.

Applicants would point out that the claims at issue have been amended and are now directed to the identification of a presence of five or eight TA repeats in the promoter, wherein the presence of five TA repeats correlates with an increased expression of a UGT gene and the presence of eight repeats correlates with a decreased expression of a UGT gene. There is no teaching or suggestion in Bosma *et al.* for one to look for a five or eight TA repeat polymorphism, or that such polymorphism would have an effect on a UGT gene promoter activity.

D. Rejection of Claims 1-62 on the Basis of Obviousness

The Action next rejects all of the pending claims over either Beutler et al. or Bosma et al. in view of Clarke et al, taking the position that Beutler and Bosma teach the method of claims 1-30 and 1-23, respectively, and that Clarke et al. teaches a method of screening individuals for variation in activity of glucuronidation of drugs and xenobiotics. The Action refers us to Section E, page 24-28, of Clarke et al. in support of this position.

In response, Applicants would first respectfully point out that the Beutler et al. reference is not available under Section 102 (a) on the basis of the enclosed declaration, and that the teachings of Bosma et al. are limited and provide no teaching or suggestion whatsoever with respect to the identification of five or eight TA repeats. More importantly, there is no teaching or suggestion in Bosma that the presence of five TA repeats would correlate with an increased expression of the UTG gene, or that the presence of eight repeats would correlate with a decreased expression. Most certainly, absent a specific teaching of a five or eight repeat promoter, and a teaching that such a promoter would have differences in terms of its promoter activity, there is no basis for arriving at a conclusion of obviousness with respect to any of the claims which specify this particular feature. This would include, at least, claims 1-30 and 70-71.

With respect to the remaining claims, it is respectfully submitted that the secondary reference relied upon the Examiner, Clarke et al., in no way teaches or suggests screening individuals for variation in activity of the glucuronidation of drugs and/or xenobiotics by looking for polymorphisms in the UDPGT promoter, nor does it teach a method for optimizing drug dosage or predicting an individual's sensitivity to drugs. The Examiner refers to Section E, page 24-28, and tables 1-3 of Clarke et al. for this proposition. However, Applicants have been unable to appreciate the relevance of either of these.

Section E refers to "Factors Affecting Uridine Diphosphate Glucuronosyltransferase Expression". The first subsection of this section refers to "Ontogeny" and is merely discussing the various developmental stages of the UDPGT enzyme activities during development in rats and humans and diseases such as hyperbilirubinaemia and "grey baby" syndrome.

The next section refers to "Induction by Xenobiotics", which merely refers to ability of certain xenobiotics to induce different types of UDPGT activity. What is striking from this section is that different types of xenobiotics enlist different types of UDPGT activities -- a finding which underscores the lack of predictability and variation from drug to drug when referring to induction of UDPGT activity.

The final section entitled "Genetic Deficiencies" relates to a review of two different animal models of various UDPGT genetic deficiencies (the low androsterone UDPGT Wistar rat and the Gunn rat), as well as a reference to the Crigler-Najjar and Gilbert syndromes. As with the foregoing two sections, Applicants have been unable to identify any teaching or suggestion in the genetic deficiencies section with refer to a method for optimizing drug dosage or method for predicting an individual's sensitivity to xenobiotics.

Therefore, with respect to Section E of Clarke et al. Applicants see no relevance whatsoever to the invention of the claims, and in particular, no relevance with respect to claims 31-62 and 70-75. Furthermore, there is simply no basis for combining Clarke et al. with the primary references, particularly with respect to these claims, and particularly in light of the fact that Clarke et al. says nothing about modifying drug dosages to account for polymorphisms in a UGT promoter. If the Examiner continues to be of the opinion that the Clarke et al. reference is somehow relevant, the Examiner is respectfully requested identify the precise language and text that is being relied upon.

The final section referred to by the Examiner is Tables 1, 2 and 3. These tables merely refer to a list of drugs that are glucuronidated in humans (Table 1), the substrate specificity of rat liver (Table 2) and the characteristics of some human liver UDPGT, in terms of their substrate recognitions (Table 3). Again, as with the sections discussed above, there is simply no basis for concluding that any of these sections or tables would suggest to one of skill in the art, alone or in combination with Bosma et al., the idea of looking for mutation in the promoter of a UDPGT enzyme gene for the purpose of optimizing drug dosage or predicting a sensitivity to a particular xenobotic.

On the contrary, the paragraph on page 26 argues strongly against a conclusion of obviousness. In the first full paragraph on page 26, the author reviews instances where one drug, such as aromatic hydrocarbons in cigarette smoke, induce the glucuronidation of a second drug, such as paracetamol. Other examples include induction of glucuronidation by indoles, which serve to inhance oxazepam glucuronidation. Such a teaching would tend to teach away from a method of optimizing drug dosage or predicting sensitivity by genetic screening or by suggesting that different drugs tend to affect metabolism of other drugs.

Likewise, turning back to the Bosma et al. reference, there is no suggestion in Bosma that the reduces expression of UDPGT has an affect on any drug metabolism whatsoever. On the contrary, that reference concerns the affects of such reduced expression on bilirubin which would not be considered a xenobiotic. Thus, there is no basis for concluding from Bosma et al. that it would be obvious to look for mutations in the UDPGT promoter as a basis for changing or modifying a drug treatment regimen or as a basis for screening for sensitivity to certain drugs. Furthermore, the absence of any correlation between promoter polymorphisms and drug